

REMARKS

Claims 49-119 are pending with entry of this amendment. Claims 114-119 being added herein. No new matter was added. Applicants respectfully request entry of the amendments which are presented pursuant to a telephone interview with Examiner Alexander on June 28, 2000. Applicants wish to thank Examiner Alexander for his courtesy during the interview.

- Claims 49-63 and 86-113 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-20 of U.S. Patent No. 5,719,060.
- Claims 49-113 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-24 of co-pending Application No. 08/068,896.
- Claims 49-55, 57, 59, 62-71, 73-74, 76, 78, 81, 84, 86-93, 95, 97, 100, 101 and 105-113 were rejected under 35 U.S.C. §102 over Applicants' allegedly admitted prior art, Breemen et al.
- Claims 49, 64 and 86 were rejected under 35 U.S.C. §102 over Applicants' allegedly admitted prior art, Stuke or Zare et al.
- Claims 56, 58, 60-61, 72, 75, 77, 79-80, 82-83, 85, 94, 96, 98-99 and 102-104 were rejected under 35 U.S.C. §103 over Breemen et al.
- Claims 50-63, 65-68 and 87-101 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Applicants' disclosure or Stuke in view of Turteltaub et al.

Support for Amendments

Support for the amendments to the claims can be found throughout the specification and the claims, as originally filed. Support for the term "macromolecule" in the amendments to claims 49, 64 and 86 can be found on, e.g., page 6, line 4, page 10, line 23, page 12, lines 1 and 9, and page 13, line 17 of the specification. Support for the term "single energy source" can be found throughout the specification. The present invention utilizes a single energy source to desorb and ionize an analyte. The amendments do not introduce new matter.

As a convenience to the Examiner, a complete set of the pending claims is attached to this response as an appendix.

Obviousness-type Double Patenting Rejections

Claims 49-63 and 86-113 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-20 of U.S. Patent No. 5,719,060. Claims 49-113 were also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application No. 08/068,896.

These rejections are traversed. First, Applicants note that the '896 application has not been allowed. Therefore, pursuant to MPEP Rule 804.IB, Applicants believe it is proper to allow this application to go to issue and to raise any double patenting issues during further prosecution of the '896 application. Furthermore, Applicants note that the '060 patent has an apparent patent term through February 17, 2015. A patent issuing from the present application would normally expire on May 28, 2013. Therefore, Applicants expect no loss in patent term as a result of filing terminal a disclaimer in the present application. Without agreeing with the substance of the Examiner's rejection and in the interest of expediting the prosecution, Applicants submit herewith a terminal disclaimer over the '060 patent.

Rejections Under 35 U.S.C. §102

A. Van Breemen et al.

Claims 49-55, 57, 59, 62-741, 76, 78, 81, 84, 86-93, 95, 97, 100, 101 and 105-113 were rejected under 35 U.S.C. §102(a) as being anticipated by Van Breemen et al. (*Intern. J. of Mass Spectr. and Ion Physics* 49:35-50 (1983)). According to the Examiner, Van Breemen et al. teach analysis by mass spectrometry involving the vaporization and ionization of a small sample of matter, using a high energy source, such as a laser. Furthermore, the Examiner states that the probe used by Van Breemen is designed to hold a Vespel (polyimide) rod tip.

A reference does not anticipate a claimed invention unless the reference discloses every element of the claimed invention. As amended, the claims are directed to desorption spectrometry systems (e.g., laser desorption/ionization mass spectrometers) comprising probes, and methods of detecting macromolecular analytes using those systems. The probes of the present invention comprise a surface, at least, that is non-metallic and a macromolecular analyte to be desorbed from the non-metallic probe surface. The Van Breemen reference fails to anticipate this invention at least because the reference fails to show a system for desorbing a macromolecular analyte. Van Breemen neither teaches or anticipates macromolecular analyte desorption.

Macromolecules are very large molecules usually comprising of smaller units linked together. Applicants refer the Examiner to the following definitions of a macromolecule:

a very large molecule having a polymeric chain structure, as in proteins, polysaccharides, and other natural and synthetic polymers. (*Dorland's Medical Dictionary*, 1990)

a molecule of colloidal size, notably proteins, nucleic acids, and polysaccharides. (*Stedman's Medical Dictionary*, 1982).

Thus, an important class of macromolecules are the large biomolecules, such as proteins, carbohydrates, fatty acids and nucleic acids, molecules that are advantageously detected with the methods and systems of the present invention.

Applicants note that Van Breemen et al. desorbs "preformed ions" (i.e., ions existing prior to exposure to an energy source, such as salts) from the probe surface using

a laser. In particular, Van Breemen describes the desorption and detection of tetramethylammonium halides. The salts that were desorbed in the Van Breemen reference were approximately 74 atomic mass units (amu). These weights are described beginning on page 44, paragraph, 4 and ending on page 45 and in Figures 5 and 6. Thus, the molecules used by Van Breemen were not macromolecules, as they did not have any of the characteristics that are generally accepted in the art, e.g., they are not "large", "of colloidal size" or "polymeric."

Applicants have amended the claims without prejudice and acquiescence to better distinguish the present invention. In view of the above comments, Applicants respectfully request that the 102 rejection be withdrawn.

B. Stuke or Zare et al.

1. Stuke (U.S. Patent 4,868,366)

Claims 49, 64 and 86 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Stuke. According to the Office Action, Stuke teaches "a time of flight mass spectrometer for the analysis of biological samples that are bound to a sample probe when inserted into the mass spectrometer." Applicants respectfully traverse this rejection.

Claims 49, 64 and 86 were not anticipated by Stuke, because every element of the claims was not disclosed by Stuke. Stuke discloses a laser mass spectrometer comprising an electrode system and an ion detector means both mounted on a support flange adapted to be sealed to a port of a vacuum apparatus. See, e.g., the cover picture and the abstract. However, there is no disclosure in Stuke, wherein a probe has a surface that comprises a non-metallic material as recited in claims 49, 64 and 86. Since Stuke does not disclose every element of the claims, Stuke does not anticipate the present invention. Thus, the rejection is improper, and withdrawal of the rejection is respectfully requested.

2. Zare et al. (U.S. Patent 4,988,879)

Claims 49, 64 and 86 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Zare et al. The Office Action states that Zare et al. teaches "a time of flight mass spectrometer for the analysis of biological samples that are bound to a sample probe when inserted into the mass spectrometer." Applicants respectfully traverse this rejection.

Zare et al. does not anticipate the presently claimed invention. For example, independent claims 49, 64 and 86 recite a method of desorbing an analyte, a system, or a method for detecting an analyte, respectively, using a single energy source that directs energy to the probe surface for "desorbing and ionizing" an analyte. By contrast, Zare et al. requires two separate energy sources: a desorption laser to desorb analytes and an ionizing laser to ionize the analytes. As stated at column 10, lines 23-30, an element of Zare et al.'s methodology is "the spatial and temporal separation and desorption and ionization. This allows one to select the energies and pulse durations for each of these two steps independently." Thus, Zare et al.'s systems and methods are completely different from the presently claimed systems and methods that use a single energy source to desorb and ionize an analyte. Applicants have amended the claims without prejudice and acquiescence to distinctly claim the present invention. Furthermore, Zare does not show the desorption of macromolecular analytes. The analytes desorbed by Zare do not fall within the definition of a macromolecule as presented on page 6 of this response. Thus, Zare et al. does not disclose every element of the claims, and Applicants respectfully request withdrawal of the rejection.

The Rejection under 35 U.S.C. §103

A. Van Breemen et al.

Claims 56, 58, 60-61, 72, 75, 77, 79-80, 82-83, 85, 94, 96, 98-99 and 102-104 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Van Breemen et al. The Examiner stated that it would have been obvious to use materials other than polyamide on the probe surface, such as glass and ceramic because these are inert materials such as the polyimide referred to in Van Breemen. Applicants traverse.

Applicants refer the Examiner to the above remarks regarding the Van Breemen reference. Applicants believe that in view of the amendments and the remarks it would not have been obvious in view of Van Breemen et al. to desorb macromolecules and, more particularly, biological macromolecules such as proteins, nucleic acids and carbohydrates, using a probe with a non-metallic surface. Whether or not it might have been obvious to replace polyimide in the particular system employed by Van Breemen et al. with either glass or ceramic is beside the point. (And Applicants do not admit any such obviousness here.) Regardless of the probe material employed, it would not have been obvious to use such probe surfaces for the desorption and detection of macromolecular analytes.

At the time of the Van Breemen et al. reference (1982), it was not possible to desorb and detect macromolecules, and in particular, biological macromolecules, using the available technology. Thus, Applicants respectfully request that the 103 rejection be withdrawn.

B. Stuke and Turteltaub

Claims 50-63, 65-68 and 87-101 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Applicants' disclosure (see pages 1-5) or Stuke further in view of Turteltaub et al. According to the Examiner, "it would have been well within the skill of the art to modify the method/apparatus taught by Applicants' disclosure (see pages 1-5) or Stuke in view of Turteltaub et al. and use affinity binding techniques to collect the samples to gain the advantages taught above." Applicants respectfully traverse the rejection.

Applicants refer the Examiner to previous arguments, which are disclosed herein. Initially, it is noted that Applicants have addressed Stuke or Turteltaub et al. in several related applications and successfully overcame all of the rejections based on these references. Moreover, it is noted the use of affinity binding techniques in mass spectrometry is not a claimed feature of the present application, contrary to the Examiner's apparent belief. Rather, claimed features include systems and methods

comprising, inter alia, a probe for a mass spectrometer with a non-metallic surface and a single energy source for desorption and ionization.

Here, obviousness has not been established, because none of the cited references or the Description of the Prior Art section in the specification disclose, inter alia, systems and methods for detecting a macromolecular analyte comprising a probe that is removably insertable into a mass spectrometer, wherein the probe surface comprises non-metallic surface as recited in the present claims. For example, the Description of the Prior Art section in the specification states that in the known prior art procedures, "a bare surface of a metallic probe tip" was used. Stuke does not even provide any description for a probe for a mass spectrometer, as it is not the focus of his invention. Turteltaub et al. fails to cure these deficiencies. Turteltaub et al. discloses using aluminum or other suitable material planchet to present samples to the ion source, not a probe with a non-metallic surface as in the present application. (See column 23, lines 45-46) Moreover, as described above, Turteltaub et al.'s methods are completely different from the present invention. Because the cited references or the Description of the Prior Art section of the present application, alone or in combination, do not teach or suggest all of the claim limitations, a prima facie case of obviousness has not been established.

In view of these comments and amendments, Applicants respectfully request the Examiner to withdraw the rejections for obviousness.

CONCLUSION

Applicants believe that there is no additional fee required to file this paper. If Applicant is in error, the Commissioner is hereby authorized to charge any required fees and/or credits by this paper and during the entire pendency of this application to Account No. 06-2375/09306611.

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 713-651-5407.

Respectfully submitted,



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APPENDIX 1 – CLAIMS AS PENDING

49. A method of desorbing a macromolecular analyte from a probe surface comprising the steps of:

(a) providing a probe that is removably insertable into a mass spectrometer, the probe having a surface for presenting the analyte to a single energy source that emits energy capable of desorbing and ionizing the analyte from the probe for analyte detection, wherein at least the surface comprises a non-metallic-material, and the analyte on the surface; and

(b) exposing the analyte to energy from the single energy source, whereby the analyte is desorbed and ionized.

50. The method of claim 49 wherein the energy source emits laser light that desorbs and ionizes the analyte to produce an ion.

51. The method of claim 50 further comprising after step (b) the steps of:

(c) modifying the analyte chemically or enzymatically while deposited on the probe surface; and

(d) repeating step (b).

52. The method of claim 50 wherein the probe surface comprises an array of locations, each location having at least one analyte deposited thereon; and step (b) comprises desorbing and ionizing a first analyte from a first location in the array; and wherein the method further comprises the step of (c) desorbing and ionizing a second analyte, from a second location in the array.

53. The method of claim 50 further comprising before step (b) the step of modifying the analyte chemically or enzymatically while deposited on the probe surface.

54. The method of claim 50 wherein the surface comprises metal coated with a synthetic polymer, glass, ceramic, a synthetic polymer or a mixture thereof.

55. The method of claim 50 wherein the surface is coated with a synthetic polymer.
56. The method of claim 50 wherein the non-metallic material is substantially porous.
57. The method of claim 50 wherein the non-metallic material is substantially non-porous.
58. The method of claim 50 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially porous material.
59. The method of claim 50 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially non-porous material.
60. The method of claim 50 wherein the probe comprises glass.
61. The method of claim 50 wherein the probe comprises ceramic.
62. The method of claim 50 wherein the probe comprises a synthetic polymer.
63. The method of claim 50 wherein the analyte comprises a protein or a peptide.
64. A system for detecting an macromolecular analyte comprising:
- a removably insertable probe having a surface for presenting the analyte to a single energy source that emits energy capable of desorbing and ionizing the analyte from the probe, wherein at least the surface comprises a non-metallic material, and the analyte on the surface;
 - a single energy source that directs energy to the probe surface for desorbing and ionizing the analyte; and
 - a detector in communication with the probe surface that detects the desorbed analyte.

65. The system of claim 64 which is a laser desorption mass spectrometer wherein:
the energy source emits laser light that desorbs and ionizes the analyte to produce an ion,
the system further comprises means for accelerating the ion to the detector,
the detector detects the ion, and
the system further comprises means for determining the mass of the ion.
66. The system of claim 64 wherein the energy source emits laser light.
67. The system of claim 64 wherein the energy source emits plasma energy or fast atoms.
68. The system of claim 64 wherein the energy source emits energy of a variety of wavelengths.
69. The system of claim 64 wherein the detector detects ions.
70. The system of claim 64 wherein the detector detects radioactivity or light.
71. The system of claim 64 further comprising means for accelerating the desorbed analyte to the detector.
72. The system of claim 65 wherein the surface is adhered to the probe magnetically.
73. The system of claim 65 wherein the surface comprises metal coated with a synthetic polymer, glass, ceramic, a synthetic polymer or a mixture thereof.
74. The system of claim 65 wherein the surface is coated with a synthetic polymer.
75. The system of claim 65 wherein the non-metallic material is substantially porous.

76. The system of claim 65 wherein the non-metallic material is substantially non-porous.

77. The system of claim 65 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially porous material.

78. The system of claim 65 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially non-porous material.

79. The system of claim 65 wherein the probe comprises glass.

80. The system of claim 65 wherein the probe comprises ceramic.

81. The system of claim 65 wherein the probe comprises a synthetic polymer.

82. The system of claim 75 wherein the porous material comprises sponge-like, polymeric, high surface areas.

83. The system of claim 76 wherein the non-porous material is selected from the group consisting of glass and polyacrylamide.

84. The system of claim 77 wherein the porous material comprises sponge-like, polymeric, high surface areas.

85. The system of claim 78 wherein the non-porous material is selected from the group consisting of glass and polyacrylamide.

86. A method for detecting a macromolecular analyte comprising the steps of:

a) providing a system comprising:

(1) a removably insertable probe having a surface for presenting the analyte to a single energy source that emits energy capable of desorbing and ionizing the analyte from the probe, wherein at least the surface comprising a non-metallic material, and the analyte on the surface;

(2) a single energy source that directs energy to the probe surface for desorbing and ionizing the analyte; and

(3) a detector in communication with the probe surface that detects the desorbed and ionized analyte;

b) desorbing and ionizing at least a portion of the analyte from the surface by exposing the analyte to energy from the single energy source; and

c) detecting the desorbed and ionized analyte with the detector.

87. The method of claim 86 wherein the system is a laser desorption mass spectrometer wherein the energy source emits laser light that desorbs and ionizes the analyte to produce an ion, the detector detects the ion and the system further comprises means for accelerating the ion to the detector, and the method further comprises determining the mass of the ion.

88. The method of claim 87 further comprising before step (b) the step of modifying the analyte chemically or enzymatically while deposited on the probe surface.

89. The method of claim 87 further comprising after step (c) the steps of:

d) modifying the analyte chemically or enzymatically while deposited on the probe surface; and

e) repeating steps b) and c).

90. The method of claim 87 wherein the probe surface comprises an array of locations, each location having at least one analyte deposited thereon; and step (b) comprises desorbing and ionizing a first analyte from a first location in the array; and wherein the method further comprises the step of:

- d) desorbing and ionizing a second analyte from a second location in the array; and
- e) detecting the desorbed and ionized second analyte with the detector.

91. The method of claim 87 further comprising the step of displaying the determined mass of the analyte.

92. The method of claim 87 wherein the surface comprises metal coated with a synthetic polymer, glass, ceramic, a synthetic polymer or a mixture thereof.

93. The method of claim 87 wherein the surface is coated with a synthetic polymer.

94. The method of claim 87 wherein the non-metallic material is substantially porous.

95. The method of claim 87 wherein the non-metallic material is substantially non-porous.

96. The method of claim 87 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially porous material.

97. The method of claim 87 wherein the probe further comprises stainless steel and wherein the surface comprises a substantially non-porous material.

98. The method of claim 87 wherein the probe comprises glass.

99. The method of claim 87 wherein the probe comprises ceramic.

100. The method of claim 87 wherein the probe comprises a synthetic polymer.

101. The method of claim 87 wherein the analyte comprises a protein or a peptide.

102. The method of claim 62 wherein the synthetic polymer comprises polystyrene, polypropylene, polyethylene, polycarbonate, or biopolymers.

103. The system of claim 81 wherein the synthetic polymer comprises polystyrene, polypropylene, polyethylene, polycarbonate, or biopolymers.

104. The method of claim 100 wherein the synthetic polymer comprises polystyrene, polypropylene, polyethylene, polycarbonate, or biopolymers.

105. The method of claim 50, wherein the analyte is a biomolecule.

106. The method of claim 50, wherein the analyte is a biomolecule from an undifferentiated sample.

107. (Once Amended) The method of claim 50, wherein the analyte is [a protein, a peptide or] a nucleic acid.

108. The system of claim 65, wherein the analyte is a biomolecule.

109. The system of claim 65, wherein the analyte is a biomolecule from an undifferentiated sample.

110. (Once Amended) The system of claim 65, wherein the analyte is a protein or [,] a peptide. [or a nucleic acid.]

111. The method of claim 87, wherein the analyte is a biomolecule.

112. The method of claim 87, wherein the analyte is a biomolecule from an undifferentiated sample.

113. (Amended Once) The method of claim 87, wherein the analyte is a protein [,] or a peptide. [or a nucleic acid.]
114. The method of claim 54, wherein the surface is coated with glass.
115. The method of claim 54, wherein the surface is coated with ceramic.
116. The method of claim 73, wherein the surface is coated with glass.
117. The method of claim 73, wherein the surface is coated with ceramic.
118. The method of claim 92, wherein the surface is coated with glass.
119. The method of claim 92, wherein the surface is coated with ceramic.
120. The method of claim 50, wherein the analyte is a carbohydrate.
121. The system of claim 65, wherein the analyte is a nucleic acid.
122. The system of claim 65, wherein the analyte is a carbohydrate.
123. The method of claim 87, wherein the analyte is a nucleic acid.
124. The method of claim 87, wherein the analyte is a carbohydrate.